

Renal Response to Environmental Toxins

by William F. Finn*

Several characteristics of normal renal function increase the risk to the kidney of damage by environmental toxins. Due to the magnitude of renal blood flow the total amount of noxious substance delivered may be disproportionately high. Furthermore, the capacity to concentrate substances within the kidney by processes of filtration, reabsorption and secretion has the potential to increase the toxicity of agents which would otherwise not lead to tissue injury. Unfortunately, there are few tests of renal function which are able to detect early functional abnormalities and which, at the same time, are suited for screening purposes by virtue of their simplicity, cost and safety. Furthermore, interpretation of the tests is complicated by adaptive changes in renal function which occur with aging and in response to other disease processes.

Environmental agents produce a wide spectrum of renal dysfunction. Acute renal damage follows exposure to glycols, organic solvents, heavy metals, diagnostic and therapeutic agents and a variety of miscellaneous substances. Chronic renal disease may take the form of isolated tubular defects as seen with cadmium, interstitial nephritis due to the ingestion of lead, or vascular damage induced by external radiation. Some forms of glomerulonephritis may also be related to environmental toxins as are certain tumors of the urinary tract.

In a somewhat different fashion, patients whose renal function is limited by the presence of pre-existing disease may manifest toxicity from substances ordinarily excreted in the urine. Particular problems exist with the patients on dialysis, as they are at considerable risk to alterations in the environment.

Introduction

The kidneys are responsible for the elimination of metabolic waste and the control of the amount and composition of the body fluids. In addition, they are important in the regulation of arterial blood pressure and produce, modify or degrade substances which affect red blood cell production, calcium balance and carbohydrate metabolism. Consequently, changes in renal function modify the internal environment of the body and the external environment of the various organ systems. Unfortunately, the kidneys are particularly prone to damage by environmental agents and toxins. As an introduction to a discussion of the patterns of injury observed and the particular substances involved, it is useful to consider several aspects of normal renal function which not only account for this predilection to damage but are also most affected by it.

Normal Renal Function

Renal Blood Flow

The kidneys are highly vascular organs with a blood flow of approximately 1000 to 1200 ml/min. This represents 20 to 25% of the cardiac output so that the kidneys are supplied with more blood per gram of tissue weight than any other organ in the body. Since the appropriate response of the kidneys to the needs of their host depends in part upon their blood supply, alterations in either the absolute amount of blood flow or its intrarenal distribution can be expected to have substantial effects on overall renal function. For example, the blood flow to the kidney is distributed in such a fashion that some 90% of the blood flows through the cortex. A reduction in outer cortical blood flow with redistribution to the inner cortex has been demonstrated in situations such as hypotension (1), hemorrhage (2), and congestive heart failure (3). Similar patterns of blood flow redistribution have been suggested to play a prominent role in the kidney's response to toxins (4). An additional response of the kidney

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minimizes changes in total blood flow which might otherwise occur with modest alterations in arterial blood pressure, circulating blood volume or peripheral vascular resistance. This is accomplished by the capacity for autoregulation, a phenomenon which results in renal vasodilatation when arterial blood pressure is reduced and vasoconstriction when blood pressure is elevated. The mechanism by which this occurs remains unsettled and as a result, the effects of environmental agents on renal autoregulation are largely unexplored.

Glomerular Filtration

The initial step in the formation of urine is the production of an ultrafiltrate of plasma. The process of filtration is one which does not require the local expenditure of metabolic energy. Unlike other capillaries, those that constitute the glomerulus are interposed between two arterioles. Consequently, the hydrostatic pressure within the glomerular capillaries is higher than it is in other capillaries. Both the afferent and efferent arterioles are capable of adjusting the level of vascular tone and thus altering the glomerular capillary hydrostatic pressure. This pressure is the main driving force for filtration. It is opposed by the colloid osmotic pressure of glomerular capillary plasma and the intracapsular hydrostatic pressure. The amount of filtrate formed is also influenced by the rate of glomerular plasma flow and the surface area and permeability characteristics of the glomerular capillary membranes. As a protein-free ultrafiltrate is formed, the protein concentration of glomerular capillary plasma rises, and a point may be reached when the forces favoring filtration equal those opposing filtration and equilibrium is obtained (5). Under these circumstances, changes in glomerular plasma flow directly influence the filtration rate (6).

Abnormalities in any of the factors governing the process of glomerular filtration may lead to a severe reduction or cessation of urine formation (7). For example, a fall in glomerular capillary hydrostatic pressure due to either preglomerular vasoconstriction, postglomerular vasodilation, or both, has been held responsible for experimental acute renal failure induced in rats by the administration of high doses of mercuric chloride (8). In contrast, data have been presented which indicate that a significant reduction in glomerular permeability occurs in rats following the administration of uranyl nitrate (9). Alternatively, the forces favoring filtration may be opposed by elevation of the intratubular hydrostatic pressure as a consequence of tubular obstruction (10).

Tubular Reabsorption and Secretion

Each minute the kidneys produce 100 to 140 ml of glomerular filtrate with an osmolality of 280 to 290 mOsm/l. On a 24-hr basis this amounts to 150 to 200 liters of filtrate and over 400,000 mOsm of solute. Under ordinary circumstances, more than 99% of the filtered solute and water is reabsorbed so that an individual on the usual mixed diet excretes the solute in amounts varying between 0.5 and 1.0 mOsm/min in a variable amount of water. The minimal and maximal amount of urine passed depends upon the dietary intake of water, endogenous water production, insensible water losses and the ability to concentrate or dilute the urine. Urine production is generally 1500 ml/day. It can be appreciated that minor changes in the fractional excretion of solute and water can result in substantial changes in the amount and composition of the body fluids. The mechanisms by which the kidneys adjust the final composition of the urine are varied and incompletely understood. Some substances which are protein-bound escape filtration only to be added to the urine by the process of tubular secretion. Other substances which are freely filtered—such as amino acids and glucose—are completely reabsorbed by the tubules. These processes generally require the expenditure of metabolic energy and are thus particularly vulnerable to the effects of toxins.

Kidneys as Endocrine Organs

Renal function is modified by several extrarenal and intrarenal hormones. The major extrarenal hormones—aldosterone, vasopressin and parathyroid hormone—modulate the excretion of sodium, water and phosphorus respectively. Intrarenal hormones such as renin, prostaglandins and kallikreins exert effects of renal blood flow, glomerular filtration and tubular function. The kidneys also produce erythropoietin which stimulates red blood cell production. They modify the chemical structure of vitamin D, thereby increasing its potency and also participate in the metabolism of several hormones such as insulin.

Tests of Renal Function

In describing renal function according to the patterns of blood flow, glomerular filtration, tubular reabsorption and secretion, it is not surprising that there is no single test of renal function. The tests employed are generally applicable to one component and do not necessarily provide information concerning others. Moreover, many of the methods are useful only in experimental situations and are not of value in clinical settings.

Renal Blood Flow

The standard method of measuring renal blood flow is the PAH clearance-extraction technique. This is a time-consuming procedure which involves infusion of a solution containing PAH at a rate designed to maintain a constant level in the plasma. This is compared to the amount excreted in the urine in a given period of time. The calculation assumes that a predictable amount of PAH is extracted from the blood during passage through the cortex of the kidney and that no PAH is extracted from blood passing through the medulla. Disease processes may markedly alter the percent extraction, and unless the PAH content of the renal venous blood is determined, this technique cannot be used as an indicator of renal blood flow.

Renal angiography requires the placement of a catheter adjacent to or in the renal arteries and the injection of radio-opaque contrast material. This technique may indicate changes of intrarenal blood flow but it is not sensitive enough to detect small changes in total renal blood flow. Moreover, it is an invasive technique which by itself may transiently alter renal function. The inert gas "washout" technique (11) involves injection through a catheter of radionuclides such as ^{85}Kr and ^{133}Xe . Gamma-camera detection of the flow of radioactivity through the kidney gives a more reliable estimation of average renal blood flow when expressed as flow per gram of tissue and, in addition, may supply information concerning the distribution of flow within the kidney. However, both acute and chronic renal failure are associated with alterations in kidney weight and size. Consequently, this technique has been criticized when these two variables have not been taken into consideration (12).

Glomerular Function

Substances which are freely filterable and are neither reabsorbed, secreted nor synthesized by the tubules may be used in the measurement of the glomerular filtration rate (13). Creatinine, a naturally occurring product of muscle metabolism, approaches these criteria and as a result is the agent of choice for routine clinical determinations. At one time the urea clearance was used as an estimate of the glomerular filtration rate. However, unlike creatinine, a variable amount of urea is passively reabsorbed from the tubular fluid and thus the urea clearance underestimates the glomerular filtration rate by a substantial margin.

In order to find more valid markers of the actual glomerular filtration rate, a number of substances with the properties mentioned above have been used in the form of intravenous infusions. Of these,

the most acceptable is inulin, a polyfructose with a molecular weight of approximately 5000, which is the standard for assessing glomerular function. More recently, radioisotopes of EDTA, sodium iothalamate and sodium diatrizoate have gained popularity.

Tubular Function

Tests designed to measure tubular function are limited in their specificity. The use of substances such as phenosulfonphthalein (PSP) which are protein-bound and are added to the urine by tubular secretory processes have been used as estimated of functioning tubular mass but are in fact greatly influenced by the magnitude of renal plasma flow (14). In similar fashion, determination of the tubular capacity for reabsorption has to take into account associated changes in the glomerular filtration rate and extracellular fluid volume.

It is possible, however, to obtain evidence of selective defects in tubular function by measurement of the excretion of substances such as amino acids, glucose, phosphate and uric acid. In addition, the responses to infusion of bicarbonate or the ingestion of ammonium chloride are useful indicators of tubular defects in acid excretion. Tests of the kidney's ability to elaborate a concentrated urine involve either water restriction or the administration of vasopressin followed by measurement of the urine specific gravity or osmolality. Tests of diluting ability rely upon the excretion of a standard water load over a given period of time.

Effects of Aging

Before attributing alterations in renal function to actual or presumed environmental toxins, one must consider both the anatomical and functional changes which occur within the kidney in association with aging and which are independent of any primary or secondary disease processes. Based on studies employing the technique of microdissection of individual nephrons it is apparent that a number of structural changes do occur (15). At birth the nephrons of the outer cortex are relatively small and incompletely differentiated when compared to the nephrons of the inner cortex. During the first year of life there is a rapid increase in the length and volume of the proximal tubule. This rate of growth slows thereafter but at age 4 years the outer nephrons have the longer proximal convoluted tubules. By age 18–20 years, maturity is reached and a plateau is reached which persists until the third or fourth decade. There then occurs an apparent shrinkage of the glomeruli and the proximal convoluted tubules. This shrinkage is gradual rather than

abrupt. It commences at approximately age 40 years and is progressive. Histologically, there are variable areas of thickening of the basement membranes of Bowman's capsule and of the convoluted tubules. Sclerosing glomeruli are present after the third decade with associated medial hypertrophy, intimal proliferation and some hyalinization of small vessels.

These anatomical abnormalities have functional correlates (16). Glomerular filtration rate and renal plasma flow decrease after age 40 years and are approximately 50% of normal by age 90 years. Tubular function also decreases as indicated by a diminished ability to concentrate the urine, by a reduction in the tubular transport of glucose and by an inability to promptly excrete an acid load. Along with the decrease in glomerular filtration, the excretion of creatinine is abnormally low. This is due to the marked reduction of muscle mass which occurs in the elderly population so that endogenous creatinine production is low. Consequently, the serum creatinine is not necessarily elevated and thus, in the elderly patient, cannot be used as an index of renal function. As an important corollary, relatively small elevations in the serum creatinine concentration may indicate severe functional impairment.

Regeneration and Compensatory Hypertrophy

In response to a loss of functional renal mass, the kidneys undergo adaptive changes which tend to minimize the potential ill effects on the internal environment of the body. For instance, when renal function is lost due to a chronic disease process, both regressive and compensatory alterations in nephron architecture occur (17). One or the other of these changes may predominate in an individual nephron although they both may be present. Micropuncture studies have indicated that there are physiological adjustments to these anatomical changes in that marked heterogeneity of nephron function can be demonstrated (18). The net effect is that overall kidney function adapts to the needs of the host (19). Eventually, these compensatory processes cannot keep up with the progression of the disease and major alterations in the internal environment occur.

In contrast, when renal tissue is lost as a consequence of trauma or surgery, the remaining normal nephrons undergo compensatory hypertrophy of both structure and function. This situation is exemplified by the response to unilateral nephrectomy in persons donating kidneys for transplantation (20, 21) and has been studied in detail in experimental

animal models (22, 23). Following nephrectomy, salt and water excretion promptly increases in the contralateral kidney with an increase of both renal blood flow and glomerular filtration rate. Tubular reabsorptive and secretory function is also altered. The kidney enlarges by a process involving both hypertrophy and hyperplasia. Differences in age, sex, and diet seem to influence the degree to which compensatory kidney growth occurs (24).

Effects of Diet

Another important consideration is the effects of diet on renal function. While malnutrition by itself does not appear to lead to an increased incidence of parenchymal renal disease, dietary inadequacy may result in developmental abnormalities in the very young and physiological defects in adults. For instance, if caloric deficiency occurs early in the growth phase when cell multiplication is rapidly taking place, the kidneys may not achieve their proper weight or number of cells. Unlike some animals in which cell multiplication continues for a period of time after birth, the human kidney has its full complement of cells and malnutrition following birth would not necessarily be expected to have an adverse effect on kidney size. There have been, however, reports that infants dying from protein-calorie malnutrition have kidneys which are smaller than normal and show signs of chronic contraction and scarring.

In adults, physiological defects predominate. These may be acute or chronic and are generally reversible. For example, fasting is associated with a natriuresis which can be abolished by refeeding with carbohydrate. The natriuresis has been related to alterations in glucagon levels (25) and the need to excrete metabolically generated anions (26). With prolonged malnutrition, although renal blood flow and glomerular filtration rate are thought to be normal, other physiological parameters may be adversely affected. In particular, the responses to salt and water loads are abnormal and are reflected in the propensity for edema formation when excess salt is available.

Renal Response to Toxic Agents

From the above discussion, several points emerge concerning the susceptibility of the kidney to toxic damage and the ability to detect these changes. First, because the blood flow to the kidney per gram of tissue weight is greater than any other organ in the body, the total amount of toxin delivered may, in similar fashion, be disproportionately high. Second, even if the toxic agents arrive at

the kidney in low concentrations, the processes of glomerular filtration, tubular reabsorption, and secretion make it likely that high concentrations will be achieved within the kidney itself. Third, the high rate of metabolic activity of kidney tubular cells—particularly when the reactions are dependent upon enzymes containing sulphydryl groups—make the kidney vulnerable to the actions of metabolic inhibitors. Fourth, the kidney also has the capacity to disassociate protein-bound substances and to alter the pH of the tubular fluid. Both these actions may increase the toxicity of otherwise innocuous substances. Unfortunately, the ability to detect these changes is limited by the relative insensitivity of the tests used to measure renal function, by the tremendous reserve possessed by the kidney and its ability to compensate for a loss of function, and by other changes occurring in response to age, diet and the presence of underlying disease.

Indeed, many of the pathological effects of environmental nephrotoxins are manifest as chronic, indolent renal disease which may be indistinguishable from that due to other processes. The identification of a particular toxic substance as the cause of the disease process is made more difficult by the latent period between exposure to the offending agent and the development of detectable abnormalities. For example, chronic renovascular disease produced by external radiation resembles, in many ways, that due to long-standing hypertension. Hydrocarbon exposure which has been suggested to play a role in the development of glomerulonephritis is overshadowed by immunological mechanisms, which are thought to be more important. Chronic interstitial nephritis, as has been reported with lead exposure, may be indistinguishable from that due to chronic pyelonephritis. Consequently, the most easily definable lesions attributable to nephrotoxins are those in which exposure to the agent immediately precedes the development of overt clinical abnormalities.

Acute Renal Disease

The list of agents which have been associated with acute toxic renal damage is extensive. Those which have received the widest attention can be separated into several categories; glycols, organic solvents, heavy metals, diagnostic and therapeutic agents and miscellaneous substances. In addition, various conditions associated with toxic-induced hemoglobinuria and myoglobinuria share a propensity for renal impairment.

Glycols

Glycols are used in solvents for plastics, in

paints, lacquers, textiles, and cosmetics and in flavoring extracts. Ethylene glycol, $(\text{CH}_2\text{OH})_2$, is an aliphatic alcohol which is colorless, odorless, and water-soluble. It is the main substance in antifreeze and may be ingested as a substitute for alcohol. It is converted to glycoaldehyde by the enzyme alcohol dehydrogenase with further metabolism to glycolic acid and glyoxylate with eventual irreversible oxidation to oxalate. Since the initial reaction is dependent upon alcohol dehydrogenase, simultaneous ingestion of ethyl alcohol will decrease the oxidation of ethylene glycol and modify the toxicity. The major manifestations of ethylene glycol poisoning involve the central nervous system, lungs and kidneys, leading to three distinct clinical stages depending upon the organ system involved (27). In the first, central nervous system abnormalities predominate with apparent drunkenness followed by somnolence, coma and death within 12 to 24 hr. The early symptoms generally coincide with the greatest amount of aldehyde production. If the patient survives, a second stage is entered which is marked by dyspnea, cyanosis, and pulmonary edema. The third state is associated with the deposition of calcium oxalate crystals within the kidney, oxaluria and the appearance of acute oliguric renal failure. Hypocalcemia is a frequent finding, presumably due to chelation of a calcium ion by oxalate. In addition, an overwhelming acidosis may be present, a major component of which is related to the development of lactic acidosis. This occurs not only because the ratio of NADH:NAD altered by the metabolism of ethylene glycol but also because there occurs a direct inhibition of the citric acid cycle further favoring the production of lactate (28). Pyridoxine deficiency markedly increases the amount of ethylene glycol metabolized to oxalate and thus adds to the toxicity. The lethal dose of ethylene glycol is 2 ml/kg which represents 0.1g/kg of oxalic acid. In addition to the calcium oxalate crystal deposition, the pathological changes within the kidney include frank tubular necrosis with severe swelling of the proximal convoluted cells, proliferative changes in the glomeruli and modification of the glomerular basement membrane. The role of calcium oxalate crystals in the pathogenesis of the renal lesion appears to be less important than the cytotoxic effects of the other metabolites of ethylene glycol. The diagnosis should be considered when there is alcohol-like intoxication without the odor of alcohol; coma with metabolic acidosis and a large anion gap; or a urinalysis demonstrating massive calcium oxalate crystalluria. Treatment is designed to correct the acidosis, prevent the manifestations of hypocalcemia, supply adequate thiamine and

pyridoxine and removal of ethylene glycol and its products by means of a forced diuresis and/or dialysis. Acutely, intravenous treatment with ethyl alcohol is effective by virtue of its competition of alcohol dehydrogenase (29).

Other potentially toxic glycols include ethylene glycol dinitrite, propylene glycol, ethylene dichloride, and diethylene glycol. The latter is a colorless liquid that has been used in the past as a medicinal vehicle in an elixir of sulfanilamide. In 1937 at least 76 persons died as a result of taking such an elixir. The majority of kidneys studied at autopsy demonstrated cortical necrosis with several hydropic tubular degeneration.

Organic Solvents

Carbon tetrachloride (CCl_4) is widely used as an industrial solvent and as a household cleaning agent. It is a volatile, heavier-than-air liquid which is toxic in concentrations greater than 100 ppm. Absorption occurs from the gastrointestinal tract following ingestion and through the lungs during exposure to vapor. Toxicity is more likely to occur when the agent is used in confined or poorly ventilated areas. Carbon tetrachloride accumulates in the highest concentrations in fat, liver, bone marrow, blood, brain and kidney. The compound is slowly eliminated from the body with over 50 percent being exhaled.

Carbon tetrachloride is soluble in alcohol, and both the hepatic and renal toxicity increases if ethyl alcohol is consumed during the period of exposure (30). Recently, a similar potentiation has been described with isopropyl alcohol (31).

Acute renal failure occurs as a consequence of either ingestion or inhalation of carbon tetrachloride and exhibits several unusual clinical manifestations (32) which tend to separate it from other forms of nephrotoxic acute renal failure. Following exposure a reduction in urine volume may not be apparent for 7 to 10 days. During this time the individual may be symptom-free but is more apt to complain of vomiting, abdominal pain, constipation, diarrhea, or fever. With a fall in urine production, weight gain, edema, and congestive heart failure are not uncommon. The oliguria generally lasts for 1 to 2 weeks. Analysis of the urine reveals more red blood cells and protein than are usually present in other forms of nephrotoxic acute renal failure. The presence of red blood cells casts may result in an erroneous diagnosis of acute glomerulonephritis. Recovery is expected.

Toluene is an aromatic hydrocarbon that has widespread industrial use as an organic solvent. Its potential for renal toxicity has been demonstrated

in those who have practiced "sniffing" of toluene-containing substances such as model glues. The maximal allowable concentration of toluene is far exceeded when these compounds are inhaled from paper bags. Although renal damage is generally mild, severe defects in the ability to excrete acid have been noted (33).

Trichloroethylene ($\text{CHCl}=\text{CCl}_2$) is chemically related to both carbon tetrachloride and chloroform and shares with them the propensity for liver and kidney damage. It has a number of industrial uses and has been used as an anesthetic agent for obstetrical patients. Acute renal failure has followed inhalation by "solvent sniffers" (34) and in those using cleaning solutions containing this agent (35).

Heavy Metals

Heavy metals have long been associated with the development of both acute and chronic renal disease. Of those reported to cause acute renal failure, the toxicity due to mercury is the best defined. Mercury exists in the form of inorganic salts and gases and organic mercury compounds. In the inorganic form, mercury is present either as the free metal or in an ionic form such as a mercurous or mercuric salt. In the organic form, the mercury is bound covalently to at least one carbon atom. The phenol and methoxymethyl compounds degrade to inorganic mercury, while the alkyl mercury compounds remain as organic compounds (36). Chronic exposure to these latter substances results in primarily central nervous system manifestations, although several distinct renal lesions have been described in organic mercury poisoning (37). Poisoning with inorganic mercury such as mercury bichloride (sublimite) was once a common identifiable cause of acute renal failure. Mercury tends to form highly undissociated linkages to sulphydryl groups, change membrane potentials and block a number of enzymatic reactions. It is absorbed from the gastrointestinal tract and bound to plasma proteins and hemoglobin and is distributed mainly in the liver and kidney. Renal excretion occurs by tubular secretion and not by glomerular filtration while some is excreted in the feces. The initial manifestations of acute mercury poisoning primarily arise from the gastrointestinal tract and include a severe burning sensation with vomiting. As excretion occurs, additional gastrointestinal tract symptoms develop. These are marked by pain, vomiting, colic, and diarrhea. In the kidney, the terminal portion of all proximal tubules are involved. Gastrointestinal bleeding is a common complication of acute renal failure due to mercury. The toxic dose of HgCl_2 is from 0.5 to 2.5 g with a mean of approximately

1.5 g. Although recovery is expected if the patient survives the initial stage and can be supported with dialysis, the development of chronic renal failure following chronic inorganic mercury poisoning has been described (38).

Other heavy metals which have been shown to produce acute oliguric renal failure include antimony, arsenic, bismuth and uranium. These agents are responsible for direct renal damage. All nephrons are affected to an equal degree although the epithelial changes are variable, ranging from simple cellular swelling to frank necrosis. Of importance is the observation that the basement membrane is left intact. Some agents may affect specific areas of the proximal tubule in a rather predictable manner. For example, the first third of the proximal tubule may be damaged by potassium chromate, the middle third by potassium chlorate and the last third by mercuric chloride and ethylene glycol.

Diagnostic and Therapeutic Agents

Iodides: A number of cases of acute renal failure have been reported to occur following oral cholecystography (39, 40) with the use of organic acids such as sodium buniodyl and iopancic acid (Telepaque). While the former has been withdrawn from the market and the toxicity from the latter is generally low, several factors seem to predispose to renal injury. Among these are the administration to elderly patients with biliary tract disease who are given large or repeated doses. Intravenous cholangiography has also been associated with acute renal failure. It has been suggested that these agents are direct tubular toxins. Of interest, however, is their propensity to cause uricosuria. The water soluble triiodinated contrast media used for intravenous or drip-infusion pyelography and aortography are occasional sources of renal insufficiency. Agents such as acetrizate salts have been replaced with iothalamate and diatrizate salts. Despite the relative safety of these substances, acute renal failure has followed excretory (41) and drip-infusion urography (42) in diabetics given combinations of sodium and meglumine diatrizates (Hypaque; Renograffin). The use of these contrast agents for high-dose aortography is also not without hazard (43-45).

Antibiotics: A number of antibiotics are nephrotoxic. As recently reviewed by Appel and Neu (46), these include the penicillins, cephalosporins, and tetracyclines along with vancomycin, polymyxin B, colistimethate, the aminoglycosides, sulfonamides, and various antituberculous and antifungal agents. Although these agents are not environmental toxins, their widespread use and potential interaction with substances that are environmental toxins necessitates their notation.

Insecticides

Nephrotoxicity has been associated with the use of two major categories of insecticides—the organophosphorous compounds and the chlorinated hydrocarbons.

Organophosphorous compounds such as Parathion are powerful inhibitors of carboxylic esterase enzymes, including acetylcholinesterase (true cholinesterase) and pseudocholinesterase. While the predominant pharmacologic and toxicologic effects of organophosphates are due to inhibition of acetylcholinesterase of the nervous system (47), there is some evidence that absorption of organophosphorus compounds may result in a variety of renal tubular disorders (48). Abnormalities in the absorption of glucose, amino acids and phosphate have been observed, along with the inability to concentrate the urine properly. It has been suggested that these abnormalities are due to organophosphate metabolites such as *p*-nitrophenols.

Chlorinated hydrocarbons such as chlordane, in contrast to the organophosphorus compounds, accumulate unchanged in human and animal tissue. They enter the body either by way of the skin or lungs. There have been reported cases of acute oliguric renal failure associated with their use (49).

Herbicides

Bipyridinium compounds such as Paraquat react with the atmospheric O_2 to form labile hydroperoxides, which in turn give off activated oxygen. Paraquat and similar bipyridilium ions are able to accept electrons from reduced nicotinamide-adenine dinucleotide and other reduced compounds and transfer them to molecular oxygen. Its toxic manifestations include prominent azotemia with evidence of renal tubular damage (50, 51).

Hemoglobinuria and Myoglobinuria

Several situations exist in which environmental stress or toxins which are not in themselves nephrotoxic produce renal damage indirectly as a result of injury to other body structures. Such a process occurs in response to severe hemolysis or muscle injury in which the liberation into the circulation of hemoglobin and myoglobin respectively has been associated with renal failure.

Hemoglobinuria

Any process which results in intravascular hemolysis, whether due to drugs, toxins, or enzymatic defects in red blood cells, will lead to the

appearance of hemoglobin in the plasma. The globin moiety of hemoglobin is bound to the α_2 globulin, haptoglobin, while heme is bound to the β_1 globulin, hemopexin. Additional amounts of oxidized heme are complexed as hematin with albumin to form methemalbumin. When the binding capacity of these substances is exceeded, free hemoglobin appears in the plasma and enters the tubular fluid by way of glomerular filtration. Here it may be excreted unchanged in the urine or reabsorbed and degraded by tubular epithelial cells with the formation of hemosiderin. In most patients, coexistent abnormalities of arterial blood pressure, circulating red blood cell mass and extracellular fluid volume prevent definition of the role of hemoglobinuria *per se* in the development of renal damage.

Hemoglobinuria may follow certain forms of strenuous exercise (52). In people with abnormalities in the amino acid sequence of the enzyme glucose 6-phosphate dehydrogenase (G-6-PD), exposure to redox compounds commonly produces hemolysis. Although acute renal failure is an unusual complication in G-6-PD deficient individuals, a striking incidence has been reported in cases of favism (53)—a condition marked by severe hemolysis following inhalation from blossoms or ingestion of fresh beans of the plant *Vicia faba*. Other forms of hemolysis which are more regularly associated with acute renal failure include that which follows incompatible blood transfusions and exposure to certain toxins such as arsine (54). This latter substance is a colorless, nonirritating gas which may be encountered by those employed in the smelting and metal refining industries. Due to its strong reducing properties, arsine combines with hemoglobin within erythrocytes and hemolysis results. Acute renal failure is the usual cause of death.

Myoglobinuria

Myoglobin is a heme pigment with a molecular weight of approximately 17,800. It is present in the sarcoplasm of striated skeletal and cardiac muscle and is liberated into the blood stream by any process which results in destruction of striated muscle. Due to its relatively small size it is readily filterable and is excreted in the urine at serum concentrations less than 15 mg/100 ml. This requires damage to at least 200 g of muscle (55). The most reliable means of identification is by acrylamide gel electrophoresis or immunoassay, particularly in the presence of an acid urine when alterations in the spectral pattern of myoglobin interferes with analysis by absorption spectrophotometry (56). A number of situations occur in which myoglobinuria is found in association with acute renal failure.

They represent a heterogeneous group of illnesses whose main similarity lies in the presence of rhabdomyolysis.

The conditions in which myoglobinuria is found have been categorized as either hereditary or sporadic. The sporadic form occurs with rhabdomyolysis precipitated by crushing injuries, ischemia, various toxins, metabolic abnormalities, progressive muscle disease or as a consequence of high-voltage electrical injuries or strenuous exercise (55). A number of cases of epidemic myoglobinuria, or so-called Haff disease (57), have been reported which were thought to be related to the ingestion of fish containing toxic industrial wastes.

Chronic Renal Disease

Environmental agents have been implicated in the production of several types of chronic renal disease. These generally follow one of several forms which can be categorized under the headings of glomerulonephritis, chronic tubular disease or interstitial nephritis.

Glomerulonephritis

There is some evidence which suggests that chronic exposure to hydrocarbons may result in a form of glomerular disease referred to as rapidly progressive glomerulonephritis (58). This process is marked by a severe proliferation of the epithelial cells of the glomerular tuft. The mechanism by which this occurs is not known; however, it is possible that toxic damage to epithelial cells or other components of glomeruli or tubules results in an antigenic stimulus with either production of antibodies directed against the glomerular basement membrane or the formation of immune complexes with subsequent deposition in glomeruli. Epithelial proliferation and crescent formation has been induced in rats by feeding *N,N'*-diacetylbenzidine (59). In a survey of patients with clinically suspected or biopsy-proven primary proliferative glomerulonephritis, a greater exposure to toxic substances, particularly hydrocarbons, was found than in patients with other forms of renal disease (60).

Tubular and Interstitial Disease

In addition to the acute effects of environmental nephrotoxins on renal tubular structure and function a number of agents produce chronic changes which are marked by abnormalities in the reabsorption or secretion of substances such as glucose, amino acids, phosphate, and uric acid. Depending upon the particular toxin involved and/or the degree

or duration of exposure, the disease process may also involve the microvascular and interstitial structure of the kidney leading to a chronic interstitial nephritis. This spectrum of injury is reflected by the effects of exposure to substances such as cadmium, lead, and external radiation.

Nephrotoxicity Due to Cadmium: In both man and experimental animals, chronic exposure to cadmium results in abnormalities of tubular function which include glycosuria, amino aciduria and hypercalciuria. Defects in the ability to maximally concentrate the urine along with an impairment of acid excretion may be noted. Protein with a molecular weight of 20,000 to 25,000 is found in the urine and may represent an inability of the kidney to metabolize light chains (61).

Exposure to cadmium is widespread. It is found in cigarette smoke, seafood, and drinking water. Its industrial use is widespread with over 10 million pounds used each year in the United States. Cadmium initially accumulates in the liver, but over a period of time there is an increase in concentration of cadmium in the kidney with peak amounts occurring at about 50 years of age. At this time approximately $\frac{1}{3}$ of the total body cadmium is in the kidneys bound by metallothionein, a protein with a molecular weight of approximately 10,000 (62). Although chronic renal failure is an uncommon manifestation of cadmium nephrotoxicity, its association with hypertension (63) may lead to more severe damage in the form of arteriolar nephrosclerosis.

Chronic Lead Nephropathy: There are three forms of lead intoxication: acute inorganic lead poisoning due to the inhalation of lead oxide; organic lead poisoning caused by the inhalation of absorption through the skin of tetraethyllead; and chronic inorganic lead poisoning due to inorganic lead in the form of lead oxide, lead carbonate or similar compounds (37). Two types of renal impairment may be found in association with chronic lead poisoning. In the first, generalized defects of proximal tubular function are manifest by the presence of aminoaciduria, glycosuria, and phosphaturia. Serum uric acid levels are generally elevated due to a defect in the tubular secretion of uric acid. The urine can be seen to contain cells with eosinophilic intranuclear inclusions composed of lead and protein. These abnormalities most often occur in children following several months of heavy lead ingestion. While rapidly reversible, it is likely that some go on to develop chronic lead nephropathy (64). This form of renal impairment is qualitatively different from that described above in that it is manifest as an indolent disease which is clinically difficult to separate from other forms of chronic, slowly progressive renal insufficiency.

Histological examination reveals a diffuse interstitial fibrosis with tubular degeneration and fibrosis of the adventitia and media of small arteries. An associated inflammatory reaction is generally absent. Of particular interest is the presence of lead-containing intranuclear inclusions within proximal tubular epithelial cells. The diagnosis is suspected when a protracted course of renal disease is associated with symmetrical contraction of both kidneys and there is evidence of prior excessive lead absorption with the absence of other definable causes of renal disease (65). More specific information is supplied by the determination of the serum lead concentration and the urinary lead excretion following a test dose of 1 gm calcium disodium edetate. In addition, the measurement of the level of erythrocyte enzyme δ -aminolevulinic acid dehydratase (ALA-O) is useful in the diagnosis. Various factors such as the amount of calcium in the diet, the presence of iron deficiency and the exposure to sunlight and vitamin D are said to influence the amount of lead absorbed and the severity of the disease. Recent data indicate that the frequency of chronic lead nephropathy has been underestimated and that current recommendations concerning the allowable exposure to lead needs to be revised (66). At the present time this level is set at 80 $\mu\text{g}/100$ ml of blood in adults and 60 $\mu\text{g}/100$ ml in children (67).

Radiation Nephritis: The dose of radiation required to produce renal damage is generally considered to be in excess of 2300 R to the whole of both kidneys when delivered within a five-week period of time (68). It is difficult to define an exact dose inasmuch as there are a number of variables which determine the renal response to radiation. For instance, age is an important determinant. Children may be more susceptible to the effects of radiation because of their particular pattern of organ growth. On the other hand, adults with pre-existing renal disease may present a greater risk. In addition, the area and technique of irradiation, the extent of perirenal fat and the concomitant administration of chemotherapeutic agents such as vincristine or actinomycin D (69) are modifying factors. While it is possible that radiation from a variety of sources such as diagnostic x-rays, the use of radioactive isotopes or radiation from atomic explosions could lead to the development of clinical nephritis, to date no such cases have been reported. Instead, most of the instances of radiation injury to the kidneys have occurred during or after a course of therapeutic deep x-ray treatment for pelvic carcinoma.

The clinical types of radiation nephritis have been separated into five categories (70-72): acute radiation nephritis; chronic radiation nephritis;

asymptomatic proteinuria; benign essential hypertension; and late malignant hypertension. Acute radiation nephritis is associated with a variable degree of proteinuria with hypertension and uremia and may occur prior to or without the development of other symptoms. After a lag period of 3 to 9 months in children or 6 to 13 months in adults, abnormalities which may appear include abnormalities in the urine sediment along with edema, hypertension and nocturia. The most severe complication is the development of malignant hypertension and it has been suggested that survival is dependent upon its prompt and proper management. Of those who recover from the effects of acute radiation nephritis, a significant proportion will develop evidence of chronic renal impairment. Chronic radiation nephritis may develop insidiously or as a complication of acute radiation nephritis. In contrast to the widespread vascular damage seen in acute radiation nephritis, chronic radiation nephritis is associated with tubular degeneration and interstitial nephritis. In other cases, asymptomatic proteinuria may be the only abnormality found although there is some suggestion that when this occurs there may be a degree of subclinical renal damage which may become apparent only when renal function is stressed. Mild elevation of the arterial blood pressure may be an isolated finding in other cases. At times it may be associated with proteinuria and may even progress to a phase of malignant hypertension. In contrast to those patients who develop malignant hypertension as a complication of acute radiation nephritis, there exists a group who may develop malignant hypertension months to years after exposure to radiation. This is particularly important to consider when one kidney has been radiated, for under these circumstances it may be curable by nephrectomy.

Carcinogenesis

Exposure to a number of aromatic amines has been associated with the development of carcinoma of the bladder (73, 74). The concept that bladder cancers could be caused by specific carcinogens was first reported in the late 19th century in men working in the aniline dye industry. It was later appreciated that disease also occurred in the rubber and electric cable industries. Moreover, the effective carcinogen was found not to be aniline but rather a metabolite of 2-naphthylamine. Other aromatic amines, such as 1-naphthylamine, 4-aminodiphenyl (xenylamine), 4-nitrodiphenyl and 4,4' diaminodiphenyl (benzidine) have been shown to be related to bladder carcinoma. Animal studies have shown that under certain circum-

stances these agents can result in ureteral and renal pelvic cancers. It appears that tumors of the lower urinary tract develop not because of an unusual sensitivity of these cells to the carcinogens but because they are exposed to high concentrations of the substances as produced during the course of excretion through the kidneys. Bladder carcinoma is thus an example of remote carcinogenesis. Data on renal parenchymal carcinogens is not as clear although renal epithelial and mesenchymal tumors have been produced in rats after the administration of dimethylnitrosamine (75, 76). Lead acetate has been used to produce a spectrum of tumors in the rat that range from adenomas to poorly differentiated carcinomas (77). Recently, transitional cell carcinoma involving either the renal pelvis or urinary bladder has been reported as a complication of analgesic abuse (78).

Special Problems of Patients on Hemodialysis

The advent of federal programs to support patients with chronic renal failure on long-term hemodialysis has added a new dimension in the delivery of health care in this country. In addition, it has created a rapidly growing patient population which is at considerable risk to alterations in the environment. Because the transport characteristics of artificial membranes do not exactly reflect those of the kidneys themselves, dietary supplementation and restriction along with modification of the constituents of the dialysate continue to be necessary. This has led to the development of a number of actual and potential problems. For example, a progressive neurological disease occurring in hemodialyzed patients and ending in death has been recently correlated with elevated central nervous system aluminum levels (79). The etiology of the high aluminum levels appeared to be related to the use of aluminum-containing antacids as phosphate binders. Although a causal relationship has not been substantiated, this observation re-emphasizes the potential of a variety of substances for producing a toxic effect when ingested in unusually large amounts.

In similar fashion, contamination of the water supply may deliver significant amounts of toxins which would ordinarily not reach the blood stream. This has most notably resulted in oxidative damage to red cells. Toxic methemoglobinemia has followed nitrate contamination of well water used to make the dialysate (80). Hemolysis has followed exposure to dialysate containing copper (81), chloramine (82), and formaldehyde (83). Untoward

reactions in hemodialysis patients have been related to the presence of excessive amounts of such substances as calcium, magnesium (84), and possibly fluoride in the water supply to prepare the dialysate.

The issue of fluoride is unusual in that it does not represent accidental contamination. Serum fluoride concentration is approximately 1 μ mole (0.02 μ g/ml) in normal adults, rising significantly in uremic patients (85). Several studies have found serum concentration of fluoride in uremic patients hemodialyzed with fluoridated water to be about ten times normal. The potential for accumulation of toxic amounts of fluoride from fluoridated water during dialysis is well appreciated. Little is known about fluoride interaction with body fluids and cellular elements, particularly soft tissue. A strong chemical bonding of fluoride to calcium and phosphorus accounts for its deposition in hard tissues, especially bone and teeth. Similar chemical affinity for other cations, principally magnesium and manganese, has been suggested as explanation for fluoride's interference in enzyme function. Renal osteodystrophy is a very common complication in patients treated with maintenance hemodialysis. Because of the many effects of fluoride on bone, several groups have attempted to discern a correlation between hyperfluoridemia and the development of bone disease.

These situations serve as examples of disease produced by exposure to toxins, albeit by unusual means, and in a particularly susceptible patient population. Whether or not any corollaries exist between them and the production of overt or subclinical disease in the general population is an issue worth considering.

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